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| EPPERSON, JON D | |
| **ART UNIT** | **PAPER NUMBER** |
| 1639 | |

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/029,304 | ELLMAN ET AL. | |
| | Examiner | Art Unit | |
| | Jon D. Epperson | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *53,65 and 66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/14/05*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

1. The Response filed August 19, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

### *Status of the Claims*

3. Claims 53, 55-57 and 60-63 were pending. Applicants canceled claims 55-57 and 60-63. In addition, claims 65 and 66 were added and claim 53 was amended. Therefore, claims 53, 65 and 66 are currently pending and examined on the merits.

### *Priority*

4. Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

This application is a CON of 09/277,461 filed 3/26/1999 (now US PAT 6,344,334), which is a CIP of 09/049,754 filed 3/27/1998 (now US PAT 6,344,330). However, both applications upon which priority is based fail to provide adequate support under 35 U.S.C. § 112, first paragraph for the claims of this application. Specifically, the Examiner cannot find support for the new subgenus of compounds that comprise a homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical covalently linked via a disulfide linkage to a straight chain alkyl of 1 to 10 carbon atoms that is substituted with an amino group. If applicant believes

this to be in error, applicant must disclose where in all of the priority documents support for this subgenus can be found.

The Examiner further notes that if the written description does not use precisely the same terms used in the current claims (e.g., does not disclose any specific examples of the claimed subgenus), the question then turns to whether the specification guides one of skill in the art to the subject matter that is currently claimed (e.g., see, *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) ("In the absence of blazemarks [that the claimed compounds were of special interest], simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenus"; see also *In re Ruschig*, 379 F.2d 990, 994-95, 154 USPQ 118, 122 (CCPA 1967) wherein the Court held that a broad generic disclosure failed to constitute a description of more narrowly claimed subject matter; see also *Fields v. Conover*, 443 F.2d 1386, 1391, 170 USPQ 276, 280 (CCPA 1971) wherein the Court stated that direction must be expressed in "full, clear, concise, and exact" language; see also *In re Ahlbrecht*, 435 F.2d 908, 911, 168 USPQ 293, 296 (CCPA 1971)). Here, the Examiner can find no such "blaze marks" that would direct a person of skill in the art to the currently claimed subgenus of disulfide compound that link a homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical to a straight chain alkyl of 1 to 10 carbon atoms that is subsisted with an amino especially library members that contain heterocyclic aromatic radicals having > 13 carbon atoms and > 6 heteroatom selected from atoms other than N, O, S, P, etc. (e.g., see New Matter Rejection below).

Therefore the filing date of the instant application is deemed to be the filing date of 60/253,629, which is **December 28, 2001**.

## Withdrawn Objections/Rejections

5. The rejections under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicants' arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

## Outstanding Objections and/or Rejections

### *Claim Rejections - 35 USC § 112, first paragraph*

6. Claims 53, 65 and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants' newly amended claims are directed to a broad genus of candidate target binding fragments (CTBF's). Although Applicants' claims have been amended to recite, for example, that the CTBF must contain an organic molecule "less than 2000 daltons" in size and comprise either a "homocyclic aromatic radical", a "heterocyclic aromatic radical" or a "heterocyclic radical", the claimed CTBF's still read on virtually an infinite number of compounds because Applicants do not limit the way in which the organic atoms can be arranged to form the claimed compounds. In addition, Applicants do not specify any target molecule. Further still, the CTBF's merely represent "candidate" target binding fragments and, as a result, are not even required to bind to the undisclosed target molecules.

In contrast, Applicants' specification provides only one working example of a CTBF drawn to a cross-linked oxime library that inhibits the interaction between gp120 and CD4 (e.g., see specification, pages 76-84, Example 1, see also figures 2 and 4 wherein the aldehyde precursors to the oxime library are disclosed).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966). In the present case, Applicants' specification provides only one example of a cross-linked oxime library that inhibits the interaction between gp120 and CD4 (see above). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous because the nature of the claimed compounds would depend on a vast number of undefined biological target molecules that do not share any common properties.

The CAFC has also stated that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." (e.g., see *University of California v. Eli*

*Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)). Here, Applicants have failed to provide a definition, structure, formula or chemical name for any of the compounds that fall within the scope of a CTBF with the exception of the oxime library. In addition, the CAFC has stated that a genus, which is set forth only in functional terms, "... is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function" (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (1997)). Here, Applicants claim CTBF's that can only be distinguished from other compounds by their function (i.e., their ability to act as a candidate target binding fragment), which was held to be impermissible in *Lilly*. Just as the generic term "cDNA" did not provide an adequate written description for the broad class of mammalian or vertebrate insulin DNA in *Lilly*, neither does the generic term "CTBF" provide an adequate written description for the broad class of currently claimed compounds because the term "CTBF" only defines what the compound does (i.e., it ability act as a candidate target binding fragment) rather than what the compound is (e.g., a chemical formula). Furthermore, adding the terminology "... is an organic molecule less than 2000 daltons and comprises a homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical", for example, does not alleviate the problem because a person of skill in the art would not be able to use this information to distinguish a small organic molecule (i.e., <2000 Da with the claimed requisite ring system), which possesses the required CTBF functionality, from a similar small organic molecule (i.e., also <2000 Da with the claimed requisite ring system) that does not. For instance, which of the small

organic molecules (<2000 Da) that contain the requisite homocyclic aromatic radical, heterocyclic aromatic radical or a heterocyclic possess this function? In fact, this case is even more egregious than *Lilly* because there is no "genetic code" to correlate the CTBF with a related molecule and/or target.

Thus, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the claimed invention. It is well settled that claiming only a result (e.g., ability to act as a prodrug) fails to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result, far beyond those means actually discovered or contemplated by the inventor, so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217 ; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

***Response***

7. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

**[1]** Applicants argue, "Figures 2 and 4 also provide 41 specific examples of CTBF radicals" (e.g., see 8/19/05 Response, page 4, paragraph 1).

**[2]** Applicants argue, "... a large number of small organic chemical compounds that serve as candidate target binding fragments are readily obtainable from commercial suppliers such as Aldrich Chemical Co." (e.g., see 8/19/05 Response, page 4, paragraph 1).

**[3]** Applicants argue, "... given the description provided in the specification and the fact that libraries of molecules for use in pharmacological assays were known in the art as of the filing date ... a lack of written description for the present claims is improper" (e.g., see 8/19/05 Response, page 4, paragraph 2).

**[4]** Applicants argue, "A general allegation of 'unpredictability in the art' is not a sufficient reason to support a rejection for lack of adequate written description." (e.g., see 8/19/05 Response, page 4, paragraph 2).

**[5]** Applicants argue, "... it is incumbent upon the Examiner to present reasons of lack of written description that will overcome a strong presumption of adequate written description" and cite MPEP § 2163.03 in support of this position (e.g., see 8/19/05 Response, pages 4-5).

**[6]** Applicants argue, "Applicants have described the CTBF as an organic molecule less than 2000 daltons and comprises a homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical", which presumably cures the previous deficiencies (e.g., see 8/19/05 Response, page 5, last paragraph).

**[7]** Applicants argue, "Figures 2 and 4, as well as the Aldrich and Sigma catalogues, demonstrate that the applicants had possession of a genus of small organic molecules" (e.g., see 8/19/05 Response, page 5, last paragraph).

**[8]** Applicants argue, "The facts of *Lilly* are clearly distinguishable from the present case ... the cDNA sequences that encoded insulin [in *Lilly*] were unknown ... In contrast ...

numerous chemical structure for species of the genus CTBF's have been known for decades" (e.g., 8/19/05 Response, page 6, paragraphs 1-2).

This is not found persuasive for the following reasons:

**[1]** The Examiner contends that figures 2 and 4 show the precursors to the oxime library used to inhibit the interaction between CD4 and gp120 and thus constitute "one" example (e.g., see newly amended rejection above). No other CTBF's are disclosed for inhibiting any other protein/ligand interaction.

**[2]** The Examiner contends that a person of skill in the art would not be able to use this information to distinguish an organic molecule, which possesses the required CTBF functionality, from an organic molecule that does not (i.e., which of the small organic molecules <2000 daltons in weight found in the Aldrich catalog that contain a homocyclic aromatic radical, heterocyclic aromatic radical or a heterocyclic possess this CTBF function?).

**[3]** Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Friers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Moreover, when there is little to no disclosure in the instant specification of the starting material or conditions under which claimed process can be carried out, this failure cannot be rectified by asserting that all disclosure related to the process is within skill of art. *Genentech Inc. v. Novo Nordisk A/S* (CA FC) 42 USPQ2d 1001 (3/13/1997). Here, Applicants never state which pharmacological assays are being relied upon and also never indicate the target molecule that would be used in the assay.

**[4]** The Examiner has never argued that a general allegation of unpredictability in the art is a sufficient reason to support a rejection for lack of adequate written description and, as a result, Applicants' arguments are moot. However, it should be further noted that "... the unpredictability of an art area alone may be enough to create a reasonable doubt as to the accuracy of statements in the specification." *Ex parte Singh*, 17 U.S.P.Q.2d 1714,1716 (B.P.A.I. 1990). Thus, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species (as is the case here i.e., a single oxime library species) usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38USPQ 189, 191 (CCPA 1938).

**[5]** The Examiner argues that this burden has been met in the newly amended rejection above.

**[6]** Here, Applicants claim CTBF's that can only be distinguished from other compounds by their function (i.e., their ability to act as a candidate target binding fragment), which was held to be impermissible in *Lilly*. Just as the generic term "cDNA" did not provide an adequate written description for the broad class of mammalian or vertebrate insulin DNA in *Lilly*, neither does the generic term "CTBF" provide an adequate written description for the broad class of currently claimed compounds because the term "CTBF" only defines what the compound does (i.e., it ability act as a candidate target binding fragment) rather than what the compound is (e.g., a chemical formula). Furthermore, adding the terminology "... is an organic molecule less than 2000 daltons and comprises a homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical", for example, does not alleviate the problem because a person of skill in the art would not be able to use this information to distinguish a small organic molecule (i.e., <2000

Da with the claimed requisite ring system), which possesses the required CTBF functionality, from a similar small organic molecule (i.e., also <2000 Da with the claimed requisite ring system) that does not. For example, which of the small organic molecules <2000 daltons in weight that contain a homocyclic aromatic radical, heterocyclic aromatic radical or a heterocyclic possess this CTBF function?

**[7]** Applicants are not claiming a "genus of small organic molecules" as purported (e.g., see newly amended claim 53). Applicants are claiming a library of candidate target biding fragments (CTBF's). There is no "CTBF category" in the Aldrich and Sigma catalogue. If Applicants believe this to be in error, Applicants should specifically point to such a section in the catalogs. Furthermore, Applicants' oxime library (e.g., figures 2 and 4) represent but one example that is not "representative" of this broad genus.

**[8]** First, the Examiner contends that Applicants' arguments are not commensurate in scope with the claims because the encompass both CTBF's to both "known" and "unknown" target molecules. Second, the CAFC has stated that a genus, which is set forth only in functional terms, "... is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function" (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (1997)). Here, Applicants claim CTBF's that can only be distinguished from other compounds by their function (i.e., their ability to act as a candidate target binding fragment), which was held to be impermissible in *Lilly*. Just as the generic term "cDNA" did not provide an adequate written description for the broad class of mammalian or vertebrate insulin DNA in *Lilly*, neither does the generic term "CTBF" provide an adequate written description for the broad class of currently claimed compounds because the term "CTBF"

only defines what the compound does (i.e., it ability act as a candidate target binding fragment) rather than what the compound is (e.g., a chemical formula). Furthermore, adding the terminology "... is an organic molecule less than 2000 daltons and comprises a homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical", for example, does not alleviate the problem because a person of skill in the art would not be able to use this information to distinguish a small organic molecule (i.e., <2000 Da with the claimed requisite ring system), which possesses the required CTBF functionality, from a similar small organic molecule (i.e., also <2000 Da with the claimed requisite ring system) that does not. For instance, which of the small organic molecules (<2000 Da) that contain the requisite homocyclic aromatic radical, heterocyclic aromatic radical or a heterocyclic possess this function? In fact, this case is even more egregious than *Lilly* because there is no "genetic code" to correlate the CTBF with a related molecule and/or target.

Accordingly, the written description rejection cited above is hereby maintained.

***Claims Rejections - 35 U.S.C. § 103***

8. Claims 53, 65 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirkpatrick (U.S. Patent 6,552,060) (Filing Date is **August 11, 1998**) (of record) and Silverman (Silverman, Richard B. The Organic Chemistry of Drug Design and Drug Action. New York: Academic Press, Inc. 1992, pages 19-23, especially Table 2.2) (of record).

For ***claims 53, 65 and 66***, Kirkpatrick (see entire document) discloses several libraries of asymmetric disulfides (e.g., see abstract; see also figures), which read on the claimed invention. For example, Kirkpatrick discloses libraries of $R^1$-S-S-$R^2$ and $R^1$-S-S-

Y-S-S-$R^2$ compounds that bind to thioredoxin reductase/thioredoxin targets (e.g., see figure 5; see also figures 9-11; see also columns 7-11; see also column 18, lines 28-36 wherein (bis)disulfides are disclosed; see also paragraph bridging columns 4-5; see also Table 3; see claims 8 and 19; see also column 5, line 5 wherein a straight chain hydroxyalkyl is disclosed; see especially column 5, line 14). In this scenario, one of the $R_1/R_2$ groups represent the CTBF that possess a small molecular weight (i.e., < 200 daltons) comprising a homocyclic aromatic radical, a heterocyclic aromatic radical and/or a heterocyclic radical (e.g., see Figures 9-11 wherein various homocyclic and/or heterocyclic rings are disclosed). The other $R^1/R^2$ group represents $R^8$ with the exception that -Cl or –OH is substituted to the linear alkyl group (e.g., see column 18, lines 28-36, "$R^1$ and $R^2$ may be for example any of the substituents shown in Fig. 9 and Fig. 10"; see also figures 9 and 10, especially figure 10, compound H wherein a linear alkyl substituted with chlorine is disclosed; see also compounds A, B, M and O). Thus, the substituted linear $R^1/R^2$ (or R/R') groups can represent <u>BOTH</u> the $R^8$ and the CTBF. Finally, Kirkpatrick also discloses a "library" in a microtiter plate (e.g., see Kirkpatrick, column 22, paragraph 1, "Using a 96 well plate [i.e., a microtiter plate] format, parallel combinatorial chemistry ... was used to synthesize a large number of unsymmetrical disulfides [i.e., a library]"; see also column 23, paragraph 1, "A second plate [i.e., microtiter plate] was used for the assessment of biological activity or as a biological screen [i.e., parallel screening using a microtiter plate]"). Furthermore, Kirkpatrick demonstrates that two or more library members can be "mixed" together in one well (e.g., see figure 5 A-C showing "mixtures" of CTBF's such as $R^1$-S-S-$R^2$, $R^1$-SH, $R^2$-SH, Trx-

S-S-$R^1$/$R^2$ etc; see also speciation, paragraph 80, wherein "exchange" conditions are disclosed that create "mixtures" of disulfides using reductive agents such as DTT; see also Examples).

Kirkpatrick differs from the claimed invention as follows:

For ***claims 53, 65 and 66***, Kirkpatrick fails to teach an -$NH_2$ substituent for the linear $R^8$ groups. Kirkpatrick only discloses -Cl and/or -OH substituents with "linear" alkyl groups (e.g., see figure 10) and -$NH_2$ substituents with "branched" alkyl groups (e.g., see claims 8 and 19).

However, Silverman teaches the following limitations that are deficient in Kirkpatrick:

For ***claims 53, 65 and 66***, Silverman (see entire document) teaches the use of "$NH_2$ substituents" as being "isosteric replacements" for both -Cl and -OH groups (e.g., see Silverman, page 19, section 4 entitled "Bioisosterism"; see also Table 2.2, entry 1a.).

It would have been prima facie obvious to one skilled in the art at the time the invention was made to substitute the -$NH_2$ group as disclosed by Silverman (e.g., see Silverman Table 2.2, entry 1a wherein -$NH_2$ is disclosed as a "classic" isostere for -OH and -Cl) for the -Cl and/or -OH substituents on the "linear" asymmetric disulfides as disclosed by Kirkpatrick (e.g., see figure 10, compound H wherein "Cl-$CH_2$-$CH_2$-$CH_2$" is disclosed) because Silverman explicitly states that such substitutions (e.g., $NH_2$ for OH or $NH_2$ for Cl) should be made as a result of their similar physical and/or chemical properties (e.g., see Silverman Table 2.2, entry 1a showing equivalence of -OH, -Cl and -$NH_2$; see also page 19, last paragraph, "Bioisosteres are substituents or groups that have

chemical or physical similarities, and which produce broadly similar biological properties"). Consequently, the "Cl-$CH_2CH_2CH_2$" disclosed by Kirkpatrick (e.g., see figure 10, compound H) would have similar chemical and/or physical properties to the same "$NH_2$-" substituted linear alkyl (i.e., $NH_2$-$CH_2CH_2CH_2$") according to the teachings of Silverman, which then falls within the scope of the claimed "straight chain alkyl of 1 to 10 carbon atoms that is substituted with an amino" (e.g., see claim 53). A person of skill in the art would have been motivated to make such substitution because Silverman explicitly states that such a substitution is "useful to attenuate toxicity or to modify the activity of a lead compound" (e.g., see Silverman, page 19, last paragraph). Finally, a person of skill in the art would have reasonably expected to be successful because Silverman teaches that these are "classic" substitutions that are routinely made by chemists of skill in the art and Kirkpatrick explicitly states that "linear" alkyl groups (e.g., see Figure 10, compounds A-C) and "amino substituted" alkyl groups (e.g., see claims 8 and 19) are preferred embodiments.

***Response***

9. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

**[1]** Applicants argue that the Examiner previously stated that Kirkpatrick does not teach a "mixture" of library members and Silverman does not make up for this deficiency (e.g., see 8/19/05 Response, page 4, paragraph 1).

**[2]** Applicants argue, "... one who has completed an introductory college level chemistry course, would clearly understand ... merely because atoms have the same number of valence electrons, they would not have significantly similar chemical properties ... [and, as a result,] the fact that $-CH_2$, $-NH_2$, -OH, -F and -Cl are listed as 'classical isoteres', does not mean that these molecules are considered by Silverman to be bioiosteres" (e.g., see 8/19/05 Response, pages 7-8).

**[3]** Applicants argue, "One of skill in the are would recognize that an alkyl substituted with $-CH_3$, $-NH_2$, -OH, F or -Cl would have different chemical properties. It is noteworthy that alkyl chlorines are insoluble in aqueous solution and are notorious carcinogens. Alkyl amines, however, are able to form hydrogen bonds with water and are, therefore, considered soluble in aqueous solutions and are not generally considered carcinogens" (e.g., see 8/19/05 Response, page 8, first full paragraph).

**[4]** Applicants argue, "Moreover there is no motivation or reasonable expectation of success in combining Silverman with Kirkpatrick. If anything, Silverman stands for the proposition that 'nonclassical bioisosteres' of Table 2.3, can be interchanged for 'lead modification' ... [and] $-NH_2$ is not described as being a bioisostere of -Cl" (e.g., see 8/19/05 Response, page 8, second full paragraph). Applicants also state in this section that if lead modification were to be relevant it would be for the purpose of modifying the CTBF not the -S-S-$R^8$ portion of the molecule.

**[5]** Applicants argue, "... the attached article by Erlanson, notes, an amine moiety is useful in a biological assay because it improves solubility ..." (e.g., see

This is not found persuasive for the following reasons:

**[1]** The Examiner contends that those remarks are not applicable to the presently amended claims and, as a result, Applicants arguments are moot. The advisory action was directed toward different issues in a different round of prosecution including a 35 U.S.C. 112, second paragraph "metes and bounds" rejection over the meaning of what the word "mixture" meant in the context of those claims. The most recent office action (i.e., non-final RCE) makes no such assertion using the same Kirkpatrick reference. In addition, the newly amended rejection above (which has been modified from it original version to more clearly address applicants' newly amended claims) makes clear that Kirkpatrick do disclose a "mixture" as the term is now being applied.

**[2]** The Examiner respectfully disagrees. The Examiner notes Applicants' "introductory level college student" remark, but refrains from commenting further on this derogatory statement. Instead, the Examiner directs the attention of Applicants to the Buchi reference (Buchi, J. "The Constitution-Effect Relationships from a New Viewpoint" Deutsche Apotheker-Zeitung **1966**, pages 1695-1700 (1-29 for English translation)), which makes clear, in contrast to Applicants' assertions, that isosteric compounds (i.e., compounds with similar peripheral electron layers, see Buchi, page 1695 (page 2 of translation), "... molecules are isosteric if their peripheral electron layers can be seen as identical") do have similar physical and/or chemical properties. For example, Buchi states, "By exchanging isosteric groups in active-ingredient molecules, it should be possible to produce effective analogs, since the electronic charge and

physical/chemical properties of such a molecule should hardly change" (e.g., see Buchi, page 1695 (pages 2 and 3 of translation)). Thus, Buchi makes clear that isosteric molecules do have similar properties and, as a result, are useful for producing effective therapeutic analogs. Furthermore, the Examiner contends that molecules with isosteric substitutions must have similar physical and/or chemical properties because, according to Buchi, "the physical/chemical properties of such a molecule should hardly change" (e.g., see above). Therefore, Applicants' assessment of the Silverman reference is not justified.

**[3]** First, the Examiner contends that Applicants' assertions are not supported in fact and are also refuted by Silverman (e.g., see Silverman, page 19, section 4 entitled "Bioisosterism"; see also Table 2.2, entry 1a showing that $-NH_2$, -OH and -Cl substituents have similar properties). Second, Applicants' arguments are not commensurate in scope with the claims. For example, Applicants state that alkyl amines form hydrogen bonds with water and are, therefore, considered soluble in aqueous solutions, but Applicants' claims are not limited to compounds that are soluble in aqueous solutions and Applicants' claims do not require that the $-NH_2$ undergo such an interaction. Furthermore, Applicants' specification does not mention the criticality of a hydrogen bond between the $-NH_2$ and the solvent.

**[4]** In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.

1992). In this case, A person of skill in the art would have been motivated to make such substitution because Silverman explicitly states that such a substitution is "useful to attenuate toxicity or to modify the activity of a lead compound" (e.g., see Silverman, page 19, last paragraph). Finally, a person of skill in the art would have reasonably expected to be successful because Silverman teaches that these are "classic" substitutions that are routinely made by chemists of skill in the art and Kirkpatrick explicitly states that "linear" alkyl groups (e.g., see Figure 10, compounds A-C) and "amino substituted" alkyl groups (e.g., see claims 8 and 19) are preferred embodiments.

In addition, a better interpretation (and one that is consistent with the Buchi reference above) is that BOTH classical and non-classical isosteres product broadly similar physiological properties. For example, Silverman states, "Nonclassical bioisosteres do not have the same number of atoms and do not fit the steric and electronic rules of the classical isosteres [i.e. classical bioisosteres], but they do produce a similarity in biological activity" (e.g., see Silverman, paragraph bridging pages 20-21). This statement does not imply that "classical isosteres" do not possess similar biological properties rather, to the contrary, the statement merely implies that "nonclassical" isosteres (i.e., molecules that would not ordinarily be expected to produce similar properties) also can produce similar biological properties just like their classical cousins. In addition, the Examiner notes that the classical isosteres come under the "Bioisosterism" heading.

Finally, the Examiner contends, "... there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention" (e.g., see MPEP § 2144). The lead

modification is for the purpose of creating a ligand that binds to thioredoxin reductase/thioredoxin targets with better physiological properties.

**[5]** Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants describe the Erlanson reference, but fail to note how this reference is used to distinguish the current invention. To the extent that Applicants are using this reference to support their previous arguments, the Examiner contends that those points have been adequately addressed in the previous sections.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

## New Rejections

### *Claim Rejections - 35 USC § 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 53, 65 and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. Claims 53, 65 and 66 were amended in the August 19, 2005 Response. However, the Examiner cannot find support for these amendments. For example, Applicants state

that support can be found in at page 33, lines 26-33 for the currently claimed "homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical" (e.g., see 8/19/05 Response, page 4, paragraph 1). However, this section only provides support for homocyclic aromatic hydrocarbon radicals having "from 6-14 carbon atoms" and heterocyclic aromatic radicals "having from 4-13 carbon atoms and from 1-6 heteroatom selected from N, O, S and P", not any homocyclic and/or heterocyclic radical. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02 (e.g., support for heterocyclic aromatic radicals having > 13 carbon atoms and > 6 heteroatom selected from atoms other than N, O, S, P, etc.). In addition, the Examiner does not find support for Applicants currently claimed subgenus of compounds that links an alkyl chain of 1 to 10 carbon atoms that is substituted with an amino group to an organic molecule less than 200 daltons and comprises a homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical.

***Claims Rejections – 35 U.S.C. 102/103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 53, 65 and 66 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Erlanson et al. (Erlanson, D. A.; Braisted, A. C.; Raphael, D. R.; Randal, M.; Stroud, R. M.; Gordon, E. M.; Wells, J. A. "Site-directed ligand discovery" *PNAS* **August 2000**, *97(17)*, 9367-9372).

For ***claims 53, 65 and 66***, Erlanson et al. (see entire document) teach the formation of a library of 8-15 disulfides with the requisite CTBF-SS-$R^8$ formula (e.g., see abstract; see also page 9368, column 2, paragraph 2, "In a typical experiment, ... a library of 8-15 disulfide containing compounds is added to ... protein-containing buffer"; see also see figure 1 wherein a library of R-C(=O)-NH-$CH_2$-$CH_2$-S-S-$CH_2$-$CH_2$-$NH_2$ compounds are disclosed with CTBF = "R-C(=O)-NH-$CH_2$-$CH_2$-" and $R^8$ = -$CH_2$-$CH_2$-$NH_2$; see also figure 3 showing different CTBF molecules containing homocyclic

aromatic and heterocyclic rings; see also page 9367, column 1, paragraph 2, "We have developed an alternative strategy to rapidly and reliably identify small soluble drug fragments (molecular weight ~ 250 Da) that bind with low affinity to a specifically targeted site on a protein or macromolecule [i.e., a CTBF]").

The product of Erlanson et al. meet all of the structural limitations of the claimed product (see above) except for the product-by-process limitations (i.e., mixing the library members together in microtiter plate as opposed to some other reaction vessel) and thus would either anticipate or render obvious the claimed library. See MPEP § 2113, "'[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." Here, Applicants' claims are drawn to a library of candidate target binding fragments (i.e., a product), but are defined by various method steps that produce said library (i.e., combining or mixing the library members in a microtiter plate) and, as a result, represent product-by-process claims. Thus, the process limitations do not appear to provide any patentable weight to the claimed invention in accordance with MPEP § 2113. One of ordinary skill would expect the product to be the same no matter how it was "mixed" and/or "combined" together.

***Conclusion***

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
October 15, 2005

PADMASHRI PONNALURI
PRIMARY EXAMINER